UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/320,156	05/26/1999	MICHAEL ROSENBLUM	D5425CIP2	4227

7590 12/01/2006

David L Parker
FULBRIGHT & JAWORSKI LLP
600 Congress Avenue Suite 2400
Austin, TX 78701

EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 12/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/320,156
Filing Date: 5/26/1999
Appellant(s): ROSENBLUM ET AL

Melissa L.Sistrunk
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 14, 2006 appealing from the Office action mailed June 14, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Rosenblum et al, Cancer Communications, 1991, vol. 3, pp. 21-27;

5,587,458	King et al	12-1996
5,650,150	Gillies et al	7-1994

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 15 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over King et al (U.S. 5,587,458) in view of Rosenblum et al (Cancer Communications, 1991, Vol. 3, pp. 21-27, cited in a previous Office action).

King et al teach conjugates of the single chain antibody, e23 (column 6, lines 58-62), which appears to be identical to the instant scFv23. King et al teach conjugation of anti-ERbB2 antibodies with anti-tumor drugs, toxins or radionuclide (column 4, lines 9-15). King et al do not specifically teach conjugation of e23 to TNF (column 8, lines 47-67).

Rosenblum et al teach that the sensitivity of tumor cells to TNF was dramatically augmented by antibody-mediated delivery to said cells (page 23, second column, lines 15-29).

It would have been prima facie obvious at the time the claimed invention was made to substitute TNF for the cytotoxic moiety in the e23 conjugates taught by King et al. One of skill in the art would have been motivated to do so by the teachings of Rosenblum et al pointing out the benefit of antibody-mediated delivery of TNF to tumor cells relative to the administration of free TNF.

Claims 15-17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over King et al (U.S. 5,587,458) and Rosenblum et al (Cancer Communications, 1991, Vol. 3, pp. 21-27) as applied to claims 15 and 19 above, and further in view of Gillies (U.S. 5,650,150). Claim 16 embodies the composition of claim 15 wherein said conjugate is a fusion protein between a scFv and TNF. Claim 17 embodies the method of claim 15 wherein said conjugate is recombinantly produced by fusing a gene encoding said scFv to a gene encoding TNF.

The combination of King et an and Rosenblum et al render obvious the compositions and pharmaceutical composition wherein the e23 antibody is chemically linked to TNF. The combination does not teach the recombinant fusion of TNF to e23.

Gillies et al teach the recombinant fusion of TNF-alpha to the heavy chain variable region of an antibody (column 11, lines 25-50). Gilles et al teach that the recombinant method is superior to the chemical conjugation because it avoids the unexpected consequences associated with chemical coupling (column 1, lines 42-51)

It would have been prima facie obvious at the time the claimed invention was made to fuse TNFalpha to the e23 antibody in lieu of chemical conjugation. One of skill in the art would have been motivated to do so by the teachings of Gillies regarding the avoidance of the unexpected consequences associated with chemical conjugation.

(10) Response to Argument

Appellant argues that King provides no motivation or suggestion to combine with another reference and certainly not Rosenblum because there is no motivation to extend the technology of King as it is successful with specific cytotoxic moieties, namely Pseudomonas exotoxin A variant PE40 as derivatives thereof. This has been considered but not found persuasive. In the instant case King et al claim an immunoconjugate comprising the single chain antibody of e23 bound to a cytotoxic moiety (claim 3 of King et al). Although King et al provides P exotoxin as a preferred embodiment of a cytotoxic moiety, this does not teach away from the use of TNF as a cytotoxic moiety. Appellant argues that the examples of toxins provided by King et al on column 8, line 47 to column 9, line 11 and column 18, line 60 to column 21, line 19 would be satisfactory and there would be no motivation to look for another source of toxins. This has been

considered but not found persuasive. King et al broadly teaches that the antibodies may be attached to cytotoxic moieties which include e.g. radio active materials, anti-cancer drugs, inhibitors of protein synthesis and agents which bind to DNA. It is particularly noted that these substances are listed as "e.g." and thus do not constitute a limiting list of agents. Appellant questions the omission of TNF from the suggested agents suggested by King et al and states that there are no cytokines included in the teaches of King et al. this has been considered but not found persuasive. One of skill in the art would know that TNF is a cytotoxin as well as a cytokine, as exemplified by Rosenblum et al. further, upon reading of claim 3 of King et al one of skill in the art would conclude that the breadth of the claim includes other cytotoxins known to have been useful in antibody directed delivery

Appellant argues that Rosenblum's teachings of a monoclonal antibody would teach away from the use of a single chain antibody. This has been considered but not found persuasive. One of skill in the art understands that it is easier to produce a single chained antibody than a whole antibody. Appellant maintains that it might only be obvious to exchange the antibody of Rosenblum for another antibody which also targets melanoma. This has been considered but not found to be persuasive. Rosenblum teaches that "antibody-mediated delivery of biological response modifiers may, in general, provide a new generation of tumor-directed agents with improved selectivity and greater biological activity" (page 26, last sentence). One of skill in the art upon reading this statement would conclude that the teachings of Rosenblum et al were not limited to the targeting of melanoma with the ZME-TNF conjugate, but were applicable to the targeting of biological response modifiers such as TNF targeted to other tumor types by virtue of an antibody.

Appellant argues that the examiner has broken the invention into two and combined the teachings of the scFv23 antibody in King et al and the teachings of the cytotoxic moiety in Rosenblum et al to come up with the instant invention via hindsight reasoning. This has been considered but not found persuasive. The claim of King et al encompasses the conjugation of the scFv23 antibody to a genus of cytotoxic agents (claim 3). Rosenblum suggest that the conjugation of the anti-melanoma antibody with TNF not be limited to such but encompasses "antibody mediated delivery of biological response modifier" which is boarder than just the targeting of melanoma with TNF. Thus, both prior art references contemplate a broader use than just the preferred embodiments disclosed therein, leaving one of skill in the art to conclude that both references suggest a scope of usage which would overlap with the instant invention.

Appellant argues that the examiner has used an assertion of "official notice" and is now required to provide documentary evidence of such. This has been considered but not found persuasive. The teachings of King et al and Rosenblum et al teach toward each other because they both contemplate a larger scope of usage than the preferred embodiments in each.

Appellant argues that because there is no suggestion to combine King and Rosenblum, there can be no motivation o combine said references with any other reference including Gillies. Appellant argues that Gillies teaches away from the subject matter of claims 15 and 19 because Gillies teaches a fusion of an antibody with TNF versus a conjugate. Appellant argues that Gillies has a earlier filing date than King and Rosenblum, but that neither King nor Rosenblum chose to use the a single chain antibody for a recombinant fusion protein. This has been considered but not found persuasive. One of ordinary skill in the art would recognize that there need not be only a single means to solve the problem of targeting TNF to tumor cells, and

whereas the fusion approach of Gillies et al provides a reliable uniform source of TNF attached to a single chain monoclonal antibody, the making of the vector for the expression of the fusion protein requires additional work. The conjugation of TNF to the single chain antibody, while being free from the set up time of making a recombinant fusion protein is subject to the variations that any chemical reaction can exhibit, which can lead to batches of conjugated proteins which can differ from each other in unintended ways, requiring a screening step to insure the integrity of the chemically conjugated product. Thus, both the conjugate and the fusion protein are useful for the targeting of a cytotoxin by means of a single chain antibody, even though there are technical drawback to either of fusion or conjugation as a means for attaching TNF.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Karen A. Canella, Ph.D.

11/24/2006

KAREN A. CANELLA PH.D
PRIMARY EXAMINER

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Conferees:

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER